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An Accessible Predictive Model for Alzheimer's Disease Based on Cognitive and Neuropathological Integration

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Abstract

Alzheimer's disease is a progressive neurodegenerative disease and a major public health concern globally in aging populations. Currently, there are limited treatments for this disease, and it not only causes irreversible cognitive decline but also imposes burdens on patients' families, caregivers, and healthcare systems. While its pathology and mechanisms have been widely studied, early identification of individuals at risk remains challenging. Conventional screening often relies on categorical thresholds, which might overlook subtler and continuous changes in cognitive functions and behaviors. This research aims to develop a predictive model that quantifies an individual's risk of Alzheimer's disease by using cognitive scores, declining trends, demographic information, and neuropathological markers, and to identify clinically interpretable risk factors. Based on the SEA-AD cohort, the researchers constructed a logistic regression model by incorporating 10 continuous variables, including four cognitive test scores, their decline slopes, age, years of education, sex, and 11 categorical variables derived from neuropathology, such as LATE and CAA, selected through correlation analysis and clinical relevance. Specifically, for selecting relevant variables, we constructed heatmaps, demonstrating all the correlations of data and finding the strongest associated ones with AD diagnosis. The model demonstrates strong discriminatory performance (AUC = 0.96). LATE Stage 3, severe arteriolosclerosis, and memory decline were associated with increased AD risk, while higher baseline memory, language test scores, and more years of education could delay the onset of dementia, as the data show. To illustrate the model's interpretability, we conducted a hypothetical case simulation by simulating a 75-year-old male with mild cognitive impairment and no advanced pathology, yielding a predicted AD risk of 6.3%. This model demonstrates the potential for AD identification at an early age,

providing a tool for individuals to test their risk of AD by using certain clinical scores and data.

Keywords

Alzheimer's Disease, Predictive Model, Cognitive Decline, Neuropathological Markers, Early Diagnosis

1. Introduction

Alzheimer's disease is the most common dementia, representing approximately 60% to 80% of total cases around the world [1]. AD usually shows symptoms of slow neurodegeneration and common clinical features, including cognitive function decline, memory loss, and changes in behavior. At the pathological level, two key features of AD are amyloid-β accumulation and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein [2] [3], which inhibit synaptic transmission and result in neuron death. These are most evident in brain areas like the hippocampus and cortex, which are important for memory and higher-level thinking. Also, several factors, such as genetics and the environment, can cause the onset of AD. The apolipoprotein E (APOE) *ε*4 allele is the most important genetic factor that could cause Alzheimer's disease (AD) [4] [5]. However, there are also important factors that are not genetic but due to environmental influences. Specifically, cerebrovascular diseases like cerebral amyloid angiopathy (CAA), atherosclerosis, and arteriolosclerosis could contribute to progression by changing blood flow in the brain and causing more neuroinflammation [6] [7]. In the early stages of AD, the symptoms are often mild cognitive decline, which is hard to distinguish from normal changes associated with aging. As the disease worsens, patients may gradually show more obvious symptoms, such as problems with motor skills, confusion, aphasia, and the inability to be independent [8]. As the world's population gets older, the number of AD patients keeps rising, making it a major public health problem. Even though we know more about how the disease works, it is still hard to diagnose it early, especially in people who are still in the early stage [9]. Most of the time, traditional diagnostic criteria use categorical cut-off points, which means that they might miss small and ongoing signals of cognitive decline. This is why creating tools or models that can detect the risk factors at an early stage is urgent, requiring a more personalized diagnosis of AD.

Alzheimer's disease is now known to be one of the biggest public health issues of the 21st century. It affects not only the person who has it, but also healthcare systems, economies, and societies all over the world. With the aging population worldwide, it is estimated that AD will triple by 2050, with more than 150 million people stricken with the disease [10] [11]. This will lead to unprecedented pressure on healthcare systems and infrastructure, laying a particular burden especially on low- and middle-income countries, where there are currently few re-

sources for the treatment of dementia and medical support [12]. The impact on the economy is also striking, with the expense of dementia-related costs exceeding $1.3 trillion annually [13] [14]. However, the impact of AD goes far beyond the economy. The family caregivers of AD patients usually undertake 70% of dementia care, facing multiple challenges in physical, emotional, and financial aspects. For example, in America, caregivers offer an estimated 18.5 billion hours of care annually, leading to economic losses from reduced workplace participation and contributions and increasing personal healthcare expenses [15]. Research indicates that rates of depression, risks of chronic disease, and even death rates increase significantly [16]. The disproportionate distribution of dementia care among family members exacerbates gender inequalities in health and economic outcomes [1]. The existing AD diagnosis and management modalities are still not comprehensive enough to cover this burgeoning issue. An estimated 75% of people with dementia across the globe have yet to receive an official diagnosis while their levels of symptoms remain at a stage most conducive to positive intervention [17] [18]. Traditional diagnostic methods that rely on categorical thresholds often fail to detect subtle cognitive changes until significant neurodegeneration has occurred, leading to the loss of critical windows for treatment, increased costs to the healthcare system, and wasted time for families to plan for the future. The development of quantitative risk assessment tools like ours represents a crucial step to address the current problems. The value of such early intervention in public health is clear. Research has demonstrated that approximately 40% of dementia can be prevented or delayed through management of modifiable risk factors [19]. Our model uses clinically accessible data to provide individualized risk assessments, offering a probable solution to the current diagnostic gap with the potential to transform AD from a disease of crisis management to one of prevention and early intervention, such as adjustments to lifestyles and drug treatments. More people focus on the prevention of Alzheimer's disease, reducing the societal burden of AD and improving the outcomes for millions of patients and their families.

One of the key challenges in detecting and managing Alzheimer's disease lies in its heterogeneous and gradual progression. The disease often begins years before obvious clinical symptoms appear, with subtle cognitive changes accumulating quietly over time. Research has shown that early AD symptoms include deficits in episodic memory, executive function, and language, which can be assessed through standardized cognitive tests like the MMSE (Mini-Mental State Examination) and MoCA (Montreal Cognitive Assessment) [20]. Neuroimaging studies reveal that pathological changes, such as amyloid-β buildup and tau pathology, typically precede clinical symptoms by 10 to 20 years [21]. These biological markers are useful, but they are often expensive and difficult to test on large groups of people, which shows that we need more accessible predictors. When figuring out how likely someone is to get Alzheimer's, cognitive test results, demographic factors, and social factors are all very important. Aging is the most important risk factor that cannot be changed. People with lower levels of education are always at

a higher risk of cognitive decline, probably because they have less cognitive reserve [22] [23]. Also, research shows that having other cerebrovascular conditions and unhealthy habits, like not exercising, not socializing, and eating poorly, can greatly increase the risk of developing and worsening Alzheimer's disease [21]. Methods that combine cognitive, demographic, and biological markers, among other things, show promise for finding people at risk for AD early in large groups.

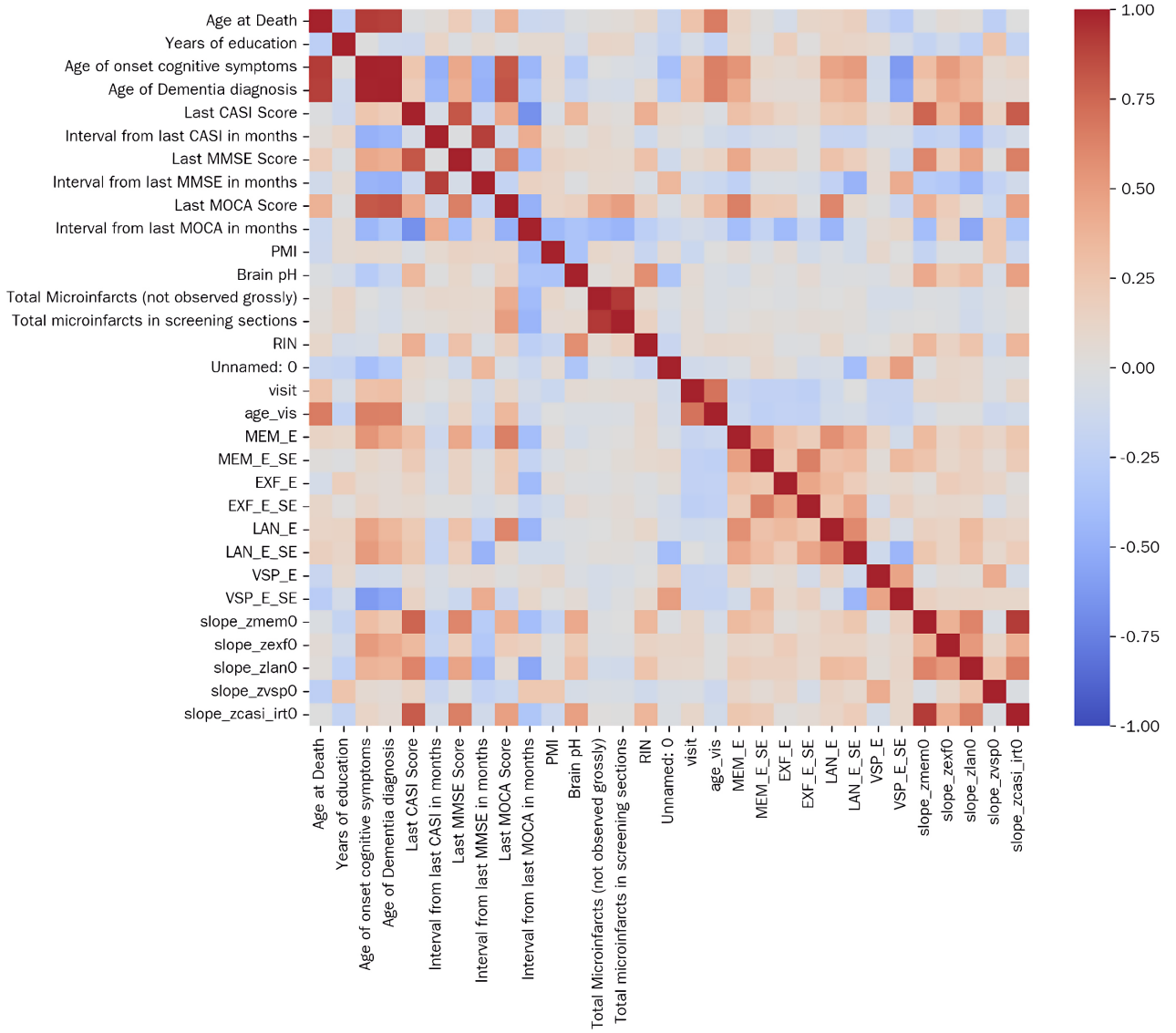
We made an AD risk predictive model in this study by using cognitive, demographic, and neuropathological data to calculate the probability of someone getting AD. The model combines continuous cognitive scores, their decline slopes, demographic factors like age and education, and neuropathological markers like LATE and CAA to give a full picture of how to find AD early. Having an AUC of 0.96 proves that this model is reliable at predicting outcomes. By incorporating important factors like memory decline, higher education, and severe neuropathological features as key indicators, the model is a significant step forward in the early diagnosis and treatment of Alzheimer's disease, as it can provide personalized and easy-to-understand risk assessments.

2. Results

Firstly, we analyzed the internal structure of our selected dataset, which contains different categories such as cognitive test scores, demographic data, and neuropathological features, to find the most relevant factors associated with Alzheimer's disease. To demonstrate how these variables are related, we created a comprehensive correlation heatmap that includes all variables in the dataset (**Figure 1**). The heatmap highlights groups of variables that particularly stand out and are related to AD, helping us select the data needed for the modeling process. There were strong positive relationships between different cognitive test scores, such as memory (MEM_E), executive function (EXF_E), and language ability (LAN_E), and their slopes of cognitive decline, such as slope_zmem0 and slope_zexf0. These correlations indicate that cognitive function factors are related to each other and could be useful for developing a model that predicts disease risk. In addition, factors such as years of education, age at visit, and neuropathological burden were linked to cognitive scores, suggesting that they could be used in the predictive model. Next, we constructed a concentrated heatmap (**Figure 2**) that only displayed the factors selected from the first heatmap. We used this to develop a logistic regression model to estimate how likely someone is to develop AD. This further refined our dataset. This stage would facilitate understanding of how variables are related and assist in selecting the final variables based on the patterns of correlation observed in the data.

To further refine our modeling approach, we constructed a focused correlation heatmap (**Figure 2**) including only the continuous predictors under consideration for the logistic regression. This allowed us to examine more clearly the internal structure among selected cognitive scores and their decline slopes. Notably, we found a strong correlation between memory and executive function (MEM_E and

EXF_E, r = 0.63), which supports their inclusion in later figures (e.g., Figure 3). Additionally, moderate correlations were observed between baseline scores and their corresponding decline slopes—such as MEM_E vs slope_zmem0 (r = 0.30) and VSP_E vs slope_zvsp0 (r = 0.42)—highlighting their clinical value in predicting future cognitive deterioration. These associations were not chosen arbitrarily but reflect stable, interpretable patterns in the data, strengthening the rationale for their role in the final predictive model.

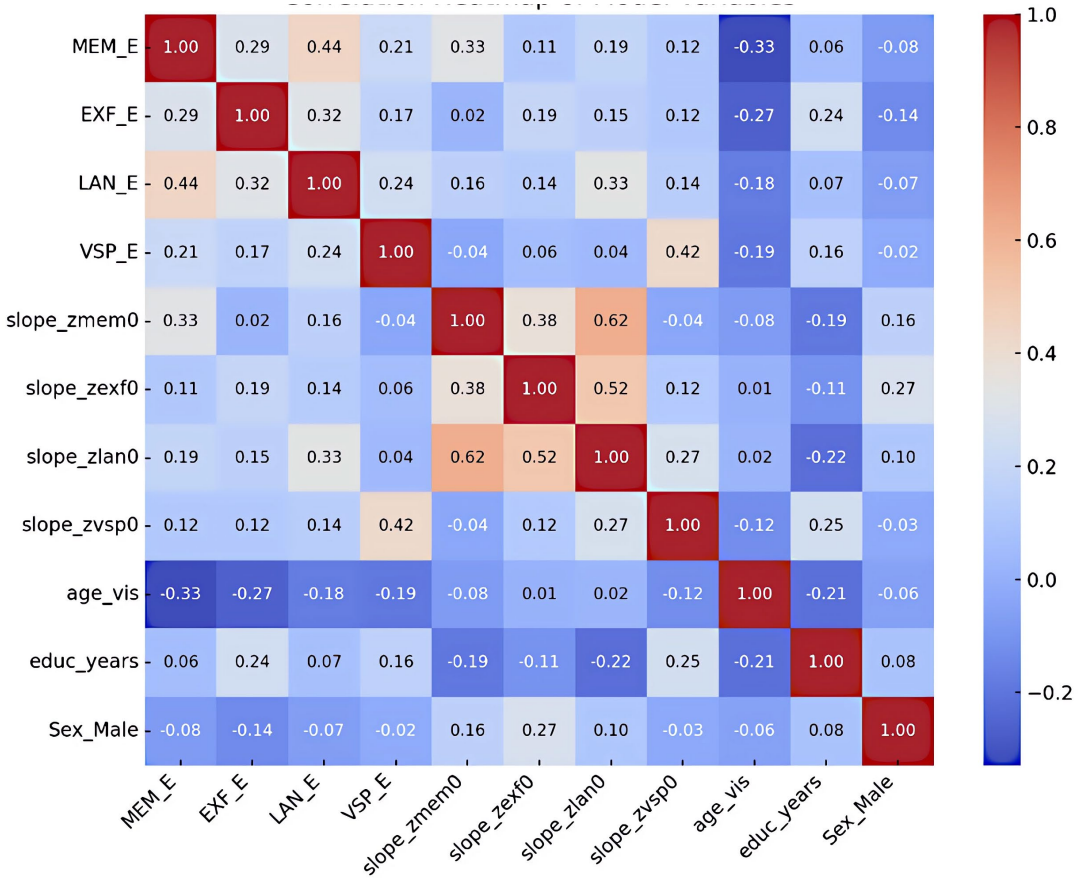


This heatmap shows Pearson correlations between continuous variables, including cognitive scores, demographics, and pathology-related measures. Red indicates positive correlation, blue indicates negative. Values range from −1 to +1. The plot reveals variable clusters useful for model selection.

Figure 1. Full correlation heatmap of all variables.

We compared the baseline memory performance of people who were diagnosed with Alzheimer's at different ages to gain a clearer picture of how significant early

cognitive state is in the clinic (Figure 3). The memory score of each person is on the x-axis, while the age at which they were diagnosed is on the y-axis. There was a clear trend: Persons who did better on memory tests were more likely to be diagnosed when they were older. This positive correlation means that a stronger memory at the beginning of the research may delay the development of clinical symptoms. This illustrates how crucial it is to undertake cognitive testing early on to find out who is at risk.

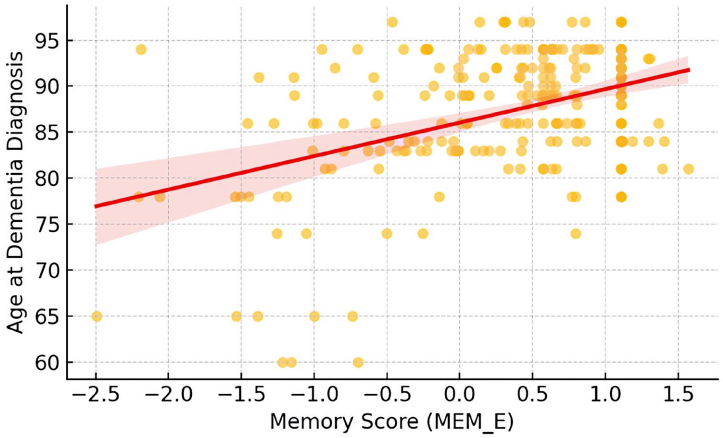


Pearson correlations among selected predictors. Warmer colors show stronger positive correlations; cooler colors show negative ones. Key pairs (e.g., MEM_E & EXF_E, VSP_E & slope_zvsp0) guided variable selection.

Figure 2. Correlation heatmap of model variables.

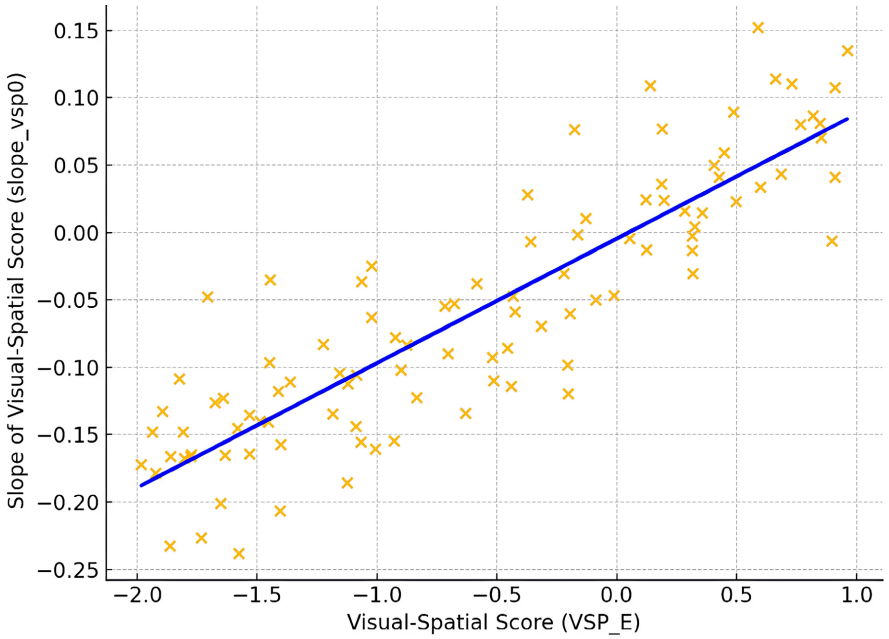
We investigate how the decrease rates (slope_zvsp0) of visual-spatial scores (VSP_E) are connected to each other (Figure 4). This helps us understand more about how cognitive performance affects future performance and how well it can predict it. There is a moderate positive association (r = 0.42), which implies that persons who are stronger at visual-spatial activities at the start tend to worsen more slowly. This trend supports the concept that cognitive status early on has long-lasting impacts and that having superior cognitive function can assist in preventing deterioration. The visualization not only helps us choose the right variables for our model, but it also offers us therapeutically meaningful confirmation

that utilizing baseline test scores to predict AD risk is a sound approach.



Each point represents one participant. Higher baseline memory scores were associated with later diagnosis age (positive correlation), suggesting that preserved cognitive function may delay clinical onset. The red line represents the linear regression fit with a 95% confidence interval.

Figure 3. Relationship between memory score (MEM_E) and age at dementia diagnosis.

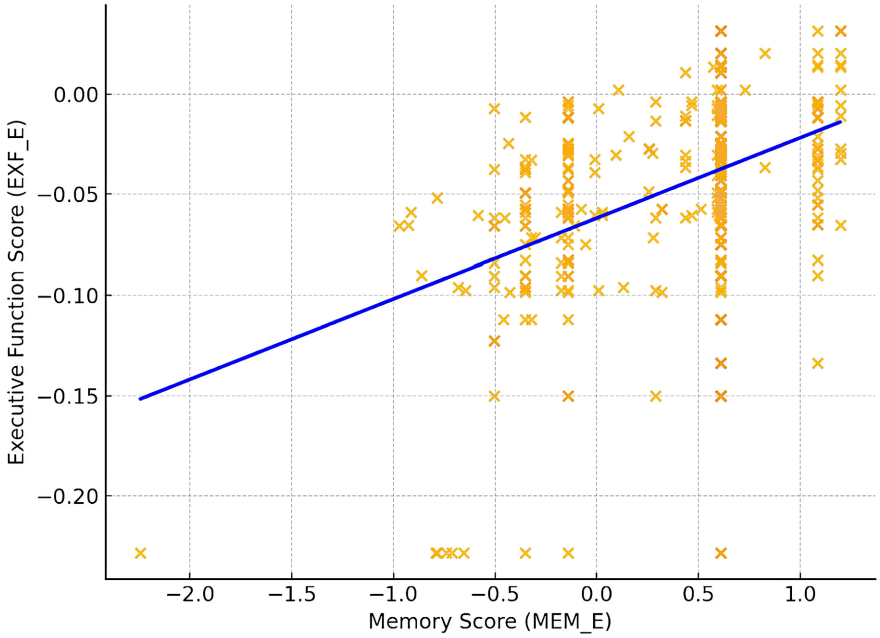


Each point represents one participant. A moderate positive correlation (r = 0.42) was observed, indicating that better baseline performance is associated with a more gradual decline in visual-spatial ability. The blue line represents the linear regression fit with a 95% confidence interval.

Figure 4. Relationship between visual-spatial score (VSP_E) and its rate of decline (slope_zvsp0).

To examine more deeply the connections across domains, we built a graph of the memory (MEM_E) and executive function (EXF_E) scores of all the partici-

pants (Figure 5). There was a strong positive trend: those who did better on memory tests also tended to do better on measures of executive function. This moderate to strong association (r = 0.63) suggests that there is a true link between these cognitive domains. This makes it seem that these regions could develop worse as Alzheimer's illness progresses. Because of this association, it is even more crucial to incorporate both measures in our model as complementary indications of baseline cognitive state.



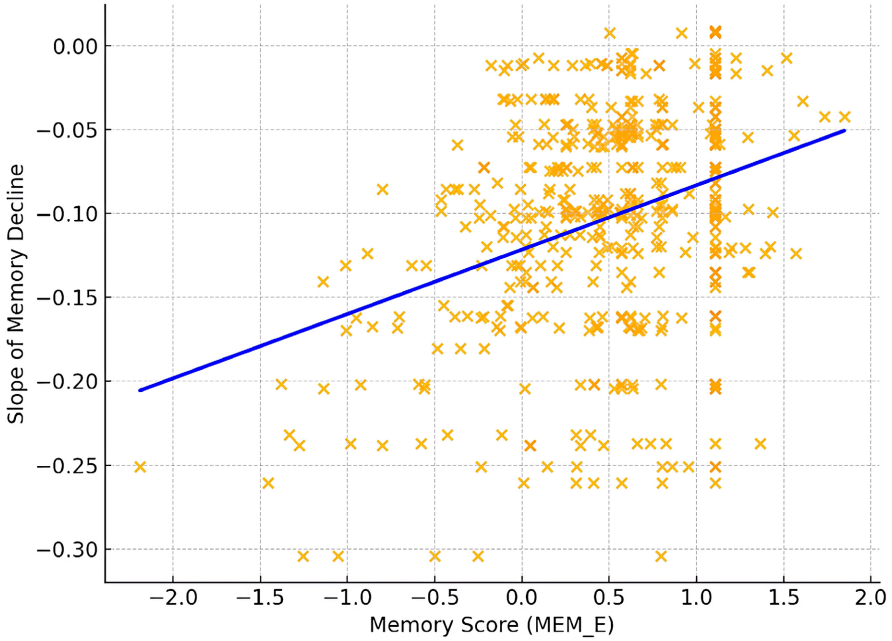
Relationship between memory score (MEM_E) and executive function score (EXF_E). Each point represents one participant. A strong positive correlation (r = 0.63) was observed, indicating that individuals with better memory performance also tend to exhibit stronger executive functioning. The blue line represents the linear regression fit with a 95% confidence interval.

Figure 5. Relationship between memory score (MEM_E) and executive function score (EXF_E).

Lastly, we examined how the memory scores at the start of the research are related to memory loss later on (Figure 6). There was a positive connection between MEM_E and slope_zmem0 (r = 0.30), which implies that those with weaker starting memory tend to lose it more quickly over time. This association is somewhat moderate, but it adds to the clinical importance of early memory assessment in predicting progression and supports our model's focus on including baseline cognitive state.

We used a mix of cognitive scores, decline slopes, demographic information, and neuropathological assessments to construct a logistic regression model that predicts how likely it is that a person will be diagnosed with Alzheimer's disease. The model has 10 predictors: 4 domain scores (MEM_E, EXF_E, LAN_E, VSP_E), their decline rates (slope_zmem0, slope_zexf0, slope_zlan0, slope_zvsp0), age,

and years of education. It also has one binary variable (Sex_Male) and 11 categorical variables based on pathology markers (CAA, arteriolosclerosis, atherosclerosis, LATE).



Each point represents one participant. A moderate positive correlation (r = 0.30) was observed, indicating that individuals with lower baseline memory scores tend to experience faster cognitive decline. The blue line represents the linear regression fit with a 95% confidence interval.

Figure 6. Relationship between memory score (MEM_E) and rate of memory decline (slope_zmem0).

With an area under the receiver operating characteristic curve (AUC) of 0.96, the model works quite well and may be used to forecast AD risks in a broad population. The model coefficients showed a number of factors that are strongly linked to the probability of AD. Specifically, having LATE Stage 3 ($\gamma = +3.16$), severe CAA ($\gamma \approx +0.66$), and severe arteriolosclerosis ($\gamma \approx +1.46$) were all highly linked to a higher risk of AD. On the other hand, greater memory and language scores (MEM_E, LAN_E) and more years of schooling were associated with a lower risk. The risk score likewise increased with age at the visit and the pace of memory loss (slope_zmem0). In order to test the efficacy of the model, we used a hypothetical scenario of a 75-year-old man with modest cognitive impairment (MEM_E = 0.5, VSP_E = 0.1), 12 years of schooling, and no advanced pathology (LATE_Not Identified = 1, CAA_Severe = 0) to operate the model and collect the outcome. The model gave a raw logistic score of −2.699, indicating that the probability of the old man developing AD was 6.3%. This example shows that the model can provide predictions that are specific and personalized to individuals and can be understood based on many different factors.

3. Discussion

Our model shows that people with higher baseline scores tended to have slower cognitive decline over time, especially in memory, language, and visual-spatial skills. This result is similar to earlier research [9], which found that memory and executive function problems starting at the early stage often happen before a formal diagnosis and predict future cognitive decline. The relationships between baseline scores and their corresponding decline slopes followed a consistent pattern instead of a random relationship [20] [21]. This shows how important they are for making the risk model to track cognitive changes over time. Additionally, the result shows that demographic factors, especially sex and education, contribute to the pattern greatly.

These data are common in clinical records, and adding them to the model can make the result more accurate, being similar to the findings of other studies that are about cognitive reserve, indicating that people who have more years of school educational experience tend to start the cognitive symptoms later [19] [20]. Putting all these factors together, including cognition, demographics, and their relationships, can help make a useful and understandable predictive risk model. While other models rely on invasive and costly tools like neuroimaging or CSF biomarkers, ours uses more readily available inputs [6] [24], which might be more realistic in large-scale screening scenarios. That said, there is room to grow. Future models could become even more precise by adding longitudinal data or context-specific factors like lifestyle or comorbid conditions. In addition to cognitive and demographic factors, our model draws attention to a less visible but crucial layer of Alzheimer's disease risk—neuropathological indicators. Among these, individuals identified with LATE Stage 3 (limbic-predominant age-related TDP-43 encephalopathy), severe arteriolosclerosis, and cerebral amyloid angiopathy (CAA) were notably more likely to receive an AD diagnosis. This was not an incidental result in our dataset; the associations appeared consistently across the sample. These findings support previous literature suggesting that mixed neuropathologies are common in late-life dementia and play a significant role in shaping clinical outcomes. LATE, for instance, has increasingly been recognized in research as a contributor to cognitive decline, particularly in older adults. Although the decline of cognitive functions is the external expression of the disease, our results suggest that these internal pathological processes are driving forces of the cognitive decline and the progression of AD. In fact, these pathology-related variables are typically available through postmortem or advanced imaging, yet our study illustrates their statistical utility even when used retrospectively. This suggests that future research might introduce proxy markers, such as blood biomarkers or genetic risk scores, to indirectly reflect pathological burden in a non-invasive way [25] [26]. By incorporating these pathological dimensions, our model builds a connection between data prediction and a mechanistic understanding of neurodegenerative diseases. It underlines the value of multifactorial modeling in AD prediction, offering not just a statistical output but a window into disease etiology

that could guide both clinical assessment and future intervention strategies.

In summary, our model, which integrates cognitive, demographic, and pathological data, offers a more holistic perspective on Alzheimer's disease risk. Rather than focusing on one factor alone, it connects various aspects, offering a more accurate reflection of how AD manifests in real life, where symptoms arise from different causes in different individuals [9]. There is biological damage, of course, but education, lifestyle, and social factors also matter [19]. Practicality is also important. Cognitive tests and education history are easy to find in most medical records, which makes this model potentially useful outside of big hospitals. In small clinics or community settings where people do not have access to brain scans or spinal fluid testing, this might be a better fit [27]. It could also be helpful for spotting people earlier—before symptoms are obvious—so that something can be done. Even basic interventions like changes in diet or sleep could matter. Additionally, it might help close gaps in care, since risk seems to vary depending on sex and educational background [22]. That said, this is not perfect. Some variables, especially the pathology ones, are hard to obtain unless there is imaging or autopsy [28]. Even the easier tests, like memory scores, may be influenced by factors such as schooling or language, which makes comparisons tricky. Logistic regression works, but it is limited—there are probably interactions or patterns we cannot see with this method. In the future, additional signals such as blood tests, genetic data, or even data from smart devices could be included. That would help. Including daily-life factors such as food, movement, or stress could also make the prediction more useful. These factors are hard to collect now, but with time and better study designs, they might become part of the solution.

4. Methods

We integrated two datasets from the SEA-AD project: harmonized cognitive scores and metadata containing demographic and neuropathological annotations. The SEA-AD cohort consists of participants from multiple clinical sites, including individuals aged 65 and above who cognitively healthy or diagnosed with mild cognitive impairment at baseline. Cognitive assessments were conducted annually over a period of 5 years, and the data includes longitudinal cognitive decline measures. The cognitive scores came from demographic and neuropathological data. The cognitive scores were derived from a series of neuropsychological assessments, and the metadata included participant demographics, such as age, years of education, and sex, as well as neuropathological features, such as cerebral amyloid angiopathy (CAA), arteriolosclerosis, atherosclerosis, and LATE. The cognitive assessment schedule followed a structured protocol, which was uniform across all recruitment sites to ensure consistency in data collection. These datasets were combined into a single dataset for analysis. The final feature set consisted of ten continuous variables: four domain scores (MEM_E, EXF_E, LAN_E, VSP_E), their respective longitudinal slopes (slope_zmem0, slope_zexf0, slope_zlan0, slope_zvsp0), age at visit (age_vis), and years of formal education.

The decline slopes were calculated using linear mixed-effects models, where individual cognitive trajectories were modeled based on multiple visits per participant. The number of visits varied between individuals, with a minimum of three assessments per individuals. We also included one binary sex variable (Sex_Male: 1 = male, 0 = female). Additionally, 11 categorical features representing neuropathological status were one-hot encoded, including staging of cerebral amyloid angiopathy (CAA), arteriolosclerosis, atherosclerosis, and LATE (limbic-predominant age-related TDP-43 encephalopathy). To ensure comparability across continuous features, all continuous features were z-standardized, transforming them to have a mean of 0 and a standard deviation of 1. This step allowed direct comparison of coefficient magnitudes across features, ensuring consistency in magnitude. We used logistic regression to model the binary outcome of clinical AD diagnosis. Logistic regression was appropriate for predicting binary outcomes, allowing us to estimate the probability of AD diagnosis based on various predictors. It provides an interpretable model of how each predictor variable influences the likelihood of an AD diagnosis, and it allow for direct comparison across studies. We considered more flexible classifiers but chose logistic regression model, as it can the results in a simplistic way, and it is supported by performance in similar studies. Model training and evaluation were performed on the full dataset (n = 504), using default regularization parameters and a maximum iteration count of 1000. Model performance was assessed by computing the area under the receiver operating characteristic curve (AUC), which indicates the model's ability to distinguish between AD-positive and AD-negative individuals. A higher AUC value reflects better discriminatory performance.

We extracted the coefficients from the logistic regression model for interpretation. The coefficients reflect the relationship between each predictor and the likelihood of an AD diagnosis. Positive coefficients suggest a higher likelihood of AD diagnosis, while negative coefficients indicate a protective effect. For example, LATE Stage 3 (coefficient = +3.16), severe CAA (coefficient = +0.66), and severe arteriolosclerosis (coefficient = +1.46) were strongly related to higher AD risk. By contrast, higher memory (MEM_E) and language (LAN_E) scores, along with more years of education, were linked to a reduced risk. This study utilizes publicly available data from the SEA-AD cohort. As the data is anonymized and publicly shared, no new informed consent was required for this study. The use of the dataset complies with the ethical guidelines provided by the data repository.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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